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BRIDGED BICYCLIC COMPOUNDS

6-PHENYL-6-ETHYL-1-AZA-4-OXABICYCLO[3.2.1]OCTAN-3-ONE AND 8-PHENYL-8-ETHYL-1,4-DIAZABICYCLO[3.2.1]OCTAN-3-ONE

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Abstract—Lactonisation of the stereoisomeric N-(carboxymethyl)-4-phenyl-4-ethylpyrrolidin-3-ols (**10a** and **b**) as well as of the corresponding methyl (**9**) and ethyl (**7**) esters and of their 3-acetates (**11**) afforded the bicyclic lactone, 6-phenyl-6-ethyl-1-aza-4-oxabicyclo[3.2.1]octan-3-one (**12**). Reductive cyclization of N-(carbethoxymethyl)-2-phenyl-2-ethylpyrrolidin-3-one oxime (**23**) yielded the bicyclic lactam, 8-phenyl-8-ethyl-1, 4-diazabicyclo[3.2.1]octan-3-one (**24**). The structures assigned to these bicyclic compounds as well as to the various pyrrolidine derivatives have been substantiated by chemical means and by the interpretation of their NMR spectra.

THE WELL ESTABLISHED physiological activity of monocyclic lactams, imides, urethans, ureides, etc., containing a quaternary carbon atom has raised the problem of the preparation of more complex molecules combining the structural features of such compounds with the increased rigidity of a bicyclic system.[1-10] The study of the biological activity of these compounds could eventually contribute to the elucidation of the mechanism underlying drug-enzyme interaction in the field of central nervous system depressants. For this purpose the title bicyclic compounds **12** and **24** have been synthesized and investigated.

Alkylation of α-phenyl-α-ethyl-β-alanine ethyl ester (**1**) with ethyl chloroacetate afforded the amino diester **2** [N-(carbethoxymethyl)-α-phenyl-α-ethyl-β-alanine ethyl ester] in 85% yield; Dieckmann condensation of the latter, in the presence of NaH in toluene, yielded 2-carbethoxy-4-phenyl-4-ethylpyrrolidin-3-one (**3**) which underwent hydrolysis and decarboxylation upon treatment with dilute HCl to give 4-phenyl-4-ethylpyrrolidin-3-one (**4**). This compound was characterised by conversion into the stable crystalline oxime derivative **5** as well as by analysis of its NMR spectrum. The latter features the expected patterns for the methylenic protons at C-2 and C-5: a double doublet centered at δ 3·24 and 3·84 (J = 12 Hz) for the C-5 protons and a singlet at δ 3·31 for the magnetically equivalent protons at C-2. The nonequivalence of the C-5 protons follows from their position next to the asymmetric center (C-4), whereas the equivalence of the C-2 protons is due to their equal deshielding by the neighbouring carbonyl. The aminic proton (singlet, δ 2·00) could be identified by exchange with D_2O. The spectrum exhibited as well the signals for the Ph and Et substituents at C-4.

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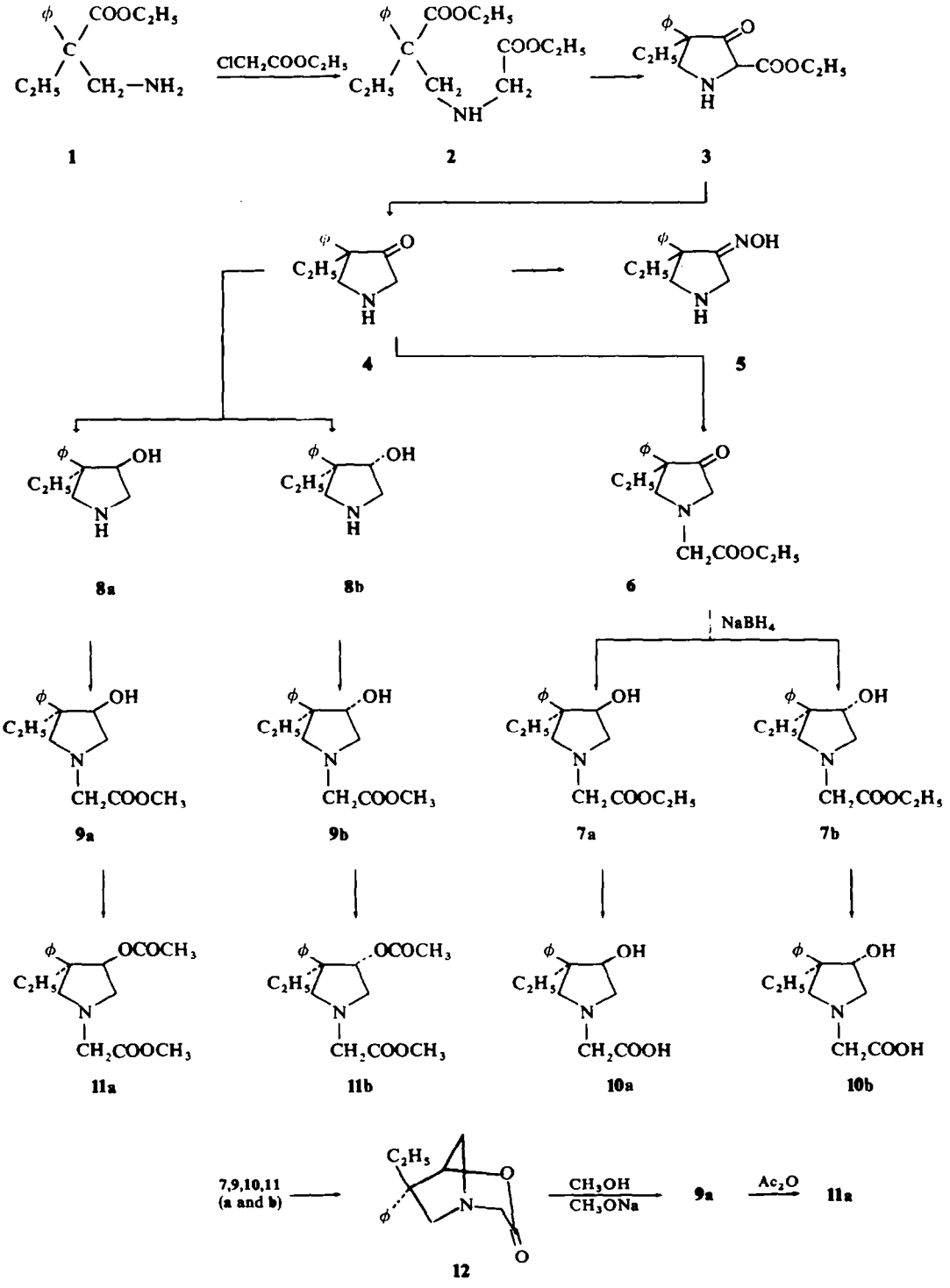
SCHEME I Synthesis of the bicyclic lactone 12



Alkylation of **4** with ethyl bromoacetate afforded the N-carbethoxymethyl derivative **6** [N-(carbethoxymethyl)-4-phenyl-4-ethylpyrrolidin-3-one], the NMR spectrum of which was diagnostic for the assigned structure; the signals of the C-2 and C-5 methylene protons possess the same pattern as in the starting compound **4** (an AB system for the C-5 protons, double doublet at δ 3·05 and 3·70, J = 9·5 Hz, and an A_2 system for the C-2 protons, singlet at δ 3·29). The methylene protons of the N-CH_2-$COOC_2H_5$ moiety are slightly nonequivalent, however only the inner bands of the expected double doublet could be visualized at δ 3·43 and 3·45.

$NaBH_4$ reduction of the keto group in **6** proceeded nonstereoselectively to give a mixture of the stereoisomeric amino-alcohols **7a** + **b** which were separated by chromatography on silicagel. The same mixture of amino-alcohols was obtained in better yield by $NaBH_4$ reduction of **4** to the amino-alcohols **8a** + **b** and subsequent N-alkylation with ethyl chloroacetate. Similarly, alkylation by means of methyl chloroacetate of the amino alcohols **8a** + **b** afforded the N-carbomethoxymethyl derivatives **9a** + **b**. The corresponding free acids **10a** + **b** were then obtained by hydrolysis of either **7** or **9**.

The complete characterisation of the related four pairs of compounds **7**, **8**, **9** and **10** was done by analysis of the NMR spectra of the N-carbomethoxymethyl derivatives **9a** + **b**, following their chromatographic separation.

TABLE 1. NMR DATA FOR COMPOUNDS **9a** AND **9b** IN $CDCl_3$

	C-2 methylene	C-3H	C-5 methylene	$NHCH_2CO$	$COOCH_3$	CH_2CH_3	CH_2CH_3
9a	2·80 dd 3·63 dd J = 11·5; 1 J = 11·5; 5	4·27 dd J = 5; 1	3·26 s	3·60 s	3·75 s	1·75 q	0·65 tr
9b	2·73 dd 3·15 dd J = 11; 2·5 J = 11; 5	4·26 dd J = 5; 2·5	AB system 3·40 d 3·00 d J = 9	3·53 s	3·74 s	1·98 q	0·60 tr

The C-2 protons couple their spins with the 3-H giving rise to an ABX system in each of the stereoisomers. In **9a** the AB part is formed by two double doublets at δ 2·80 and 3·63 with coupling constants of 11·5 Hz (J_{AB}) and 5 and 1 Hz (J_{AX} and J_{BX} respectively), whereas the X part of the system is a double doublet at δ 4·27. The corresponding ABX system in **9b** exhibits the same pattern, however with significantly different coupling constants (J_{AB} 11 Hz, J_{AX} and J_{BX}, 5 and 2·5 Hz, respectively).

The difference between the stereoisomers **9a** and **9b** is further substantiated by the pattern of the C-5 methylene: an A_2 singlet (δ 3·26) in **9a**, as compared to an AB double doublet in **9b** (δ 3·00 and 3·40; J = 9 Hz). The appearance of the C-5 methylene as a singlet in **9a** is even more peculiar if one considers the fact that this carbon is adjacent to the asymmetric C-4 which induced a magnetic nonequivalence in the C-5 protons in all other compounds of this series.

The final stereochemical assignments of the α-amino-alcohols **9a** and **9b** could be made following their conversion into the corresponding acetates **11a** and **11b**. In **11a** the *cis* Ph and AcO substituents are eclipsed, thus placing the Me of the Ac group above the plane of the aromatic ring, leading therefore to a strong shielding of its

resonance line (δ 1·65). Although the Ac group may probably freely rotate about the N—CO bond, the most populated conformer seems to be that corresponding to maximum orbital overlap between the Ph ring and the carbonyl, with the positive end of the latter towards the aromatic π electrons.

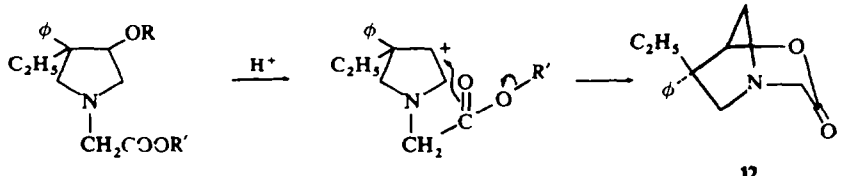
As expected, the exceptional shielding of the acetate in **11a** is counterbalanced by the "normal" position of the corresponding group in **11b** (*trans* relationship between Ph and OAc) resonating at δ 2·15. It is useful to mention that the C-5 protons in the acetates preserved the same pattern as in the corresponding alcohols (singlet at δ 3·24 in **11a** and double doublet at δ 2·95 and 3·44, J = 9·5 Hz in **11b**).

Similar behaviour has been encountered[11] in the *cis* and *trans* 2-methyl-1-phenyl-cyclopentanols; when the Ph ring is *cis* towards the Me group, the latter resonates at δ 0·47, whereas its resonance position in the *trans* isomer is 0·78.

The above assignments have been confirmed by running the NMR spectra of **11a** and **11b** in benzene, when the singlets of the Me acetates appeared at δ 1·40 and 1·74, respectively. The high field position of this signal in the *cis* compound (**11a**) is due to the cumulation of two effects: the first due to the intramolecular Ph group which manifested itself even in the nonaromatic solvent and the other due to the collision complex between the carbonyl and the aromatic solvent. By extension, compounds **7**, **9** and **10** designated by **a** are the *cis* isomers (Ph and OH) and those designated by **b** are the *trans* isomers.

Treatment with H_2SO_4 of the free hydroxyacids **10**, as well as of the hydroxyesters **7** and **9**, or the acetoxy esters **11**, in both the *cis* and *trans* series, afforded the bicyclic lactone **12** in poor yield (~ 11 %). The structure of the latter has been established by analysis of its spectral data as well as by methanolysis of the ester linkage in presence of a catalytic amount of NaOMe, thus obtaining only the *cis* hydroxyester **9a**. Since the bond opened under the reaction conditions was obviously the lactone C—O bond, the only structure assignable to the bicyclic lactone **12** is that represented by the drawn formula (6-*endo*-phenyl-6-*exo*-ethyl-1-aza-4-oxabicyclo [3. 2. 1] octan-3-one).

The fact that the same lactone was obtained from either the *cis* or the *trans* compounds, suggests that the lactonisation involves first the protonation of the 3-OH with subsequent elimination of water and creation of a positive center at C-3; intramolecular nucleophilic attack by the carbonyl leads then to the formation of the bicyclic lactone.[12]



R = H, Ac
R' = H, CH_3, C_2H_5

12

Structure **12** is in agreement with the molecular weight of the compound (231, by mass spectrometry) and the IR absorption band for the lactonic carbonyl (1720 cm^{-1}). The characterisation could be completed by analysis of the NMR spectrum (100 MHz). The C-2 protons centered at δ 3·35 and 3·85 form an AB system with a

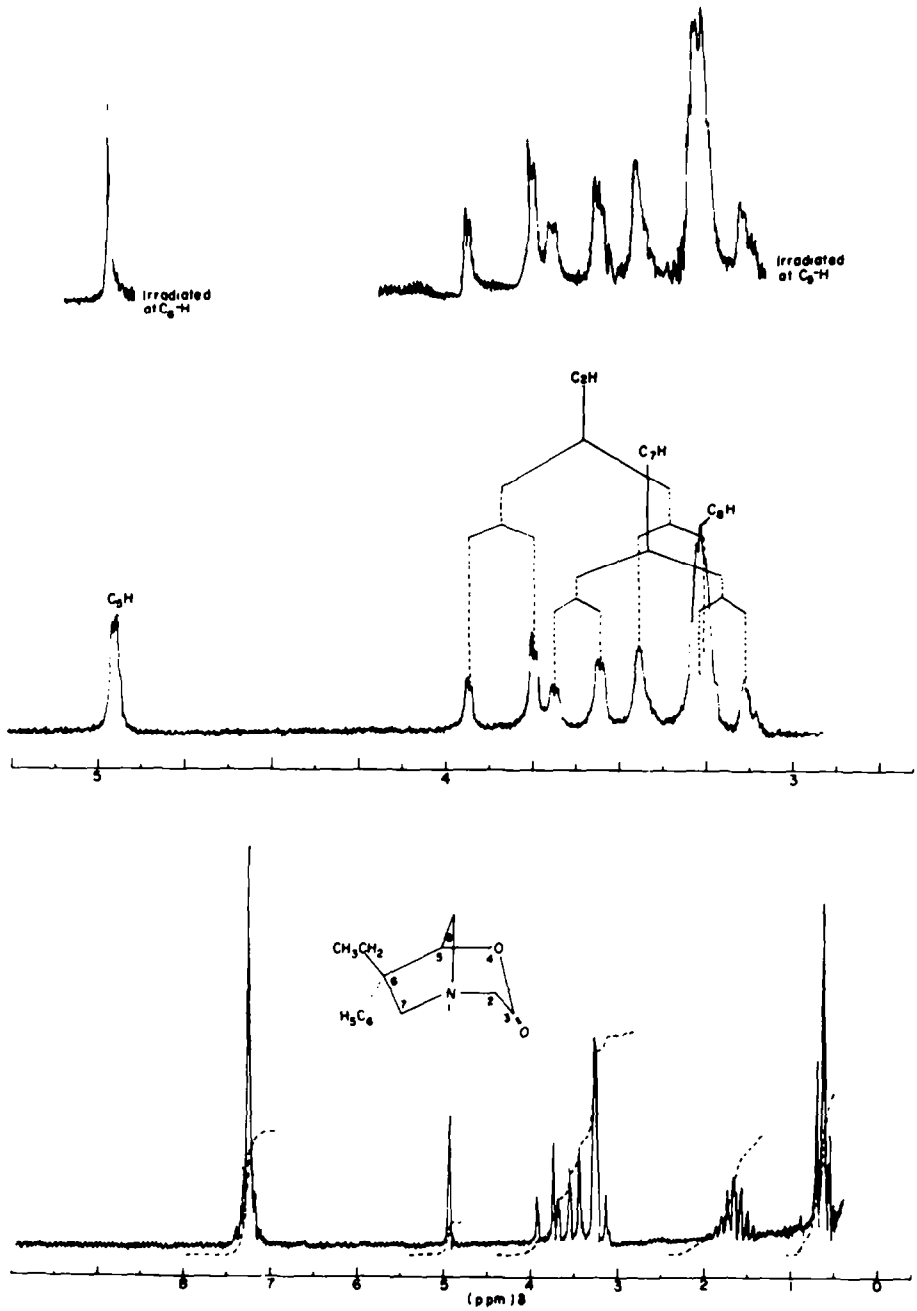


FIG 1. The NMR spectrum (100 MHz) of 6-phenyl-6-ethyl-1-aza-4-oxabicyclo [3. 2. 1] octan-3-one (**12**), in $CDCl_3$.

very large coupling constant (J = 18 Hz); the C-7 protons constitute as well an AB system at δ 3·19 and 3·62 (J = 13 Hz). The other ring protons give rise to an ABX pattern in which the bridgehead proton (5-H) couples its spin with the C-8 methylenic protons: the 5-H appears as a very narrow multiplet at δ 4·95, whereas the C-8 protons give rise to a narrow multiplet which could not be accurately characterised due to partial overlap with other signals (Fig. 1). The interrelation between these protons has been substantiated by double resonance: irradiation at the resonance position of the C-8 methylene (δ 3·27) induces the collapse of the 5-H multiplet to a sharp singlet; conversely, irradiation at the position of the latter leads to a marked simplification of the C-8 multiplet which remains however obscured by other signals.

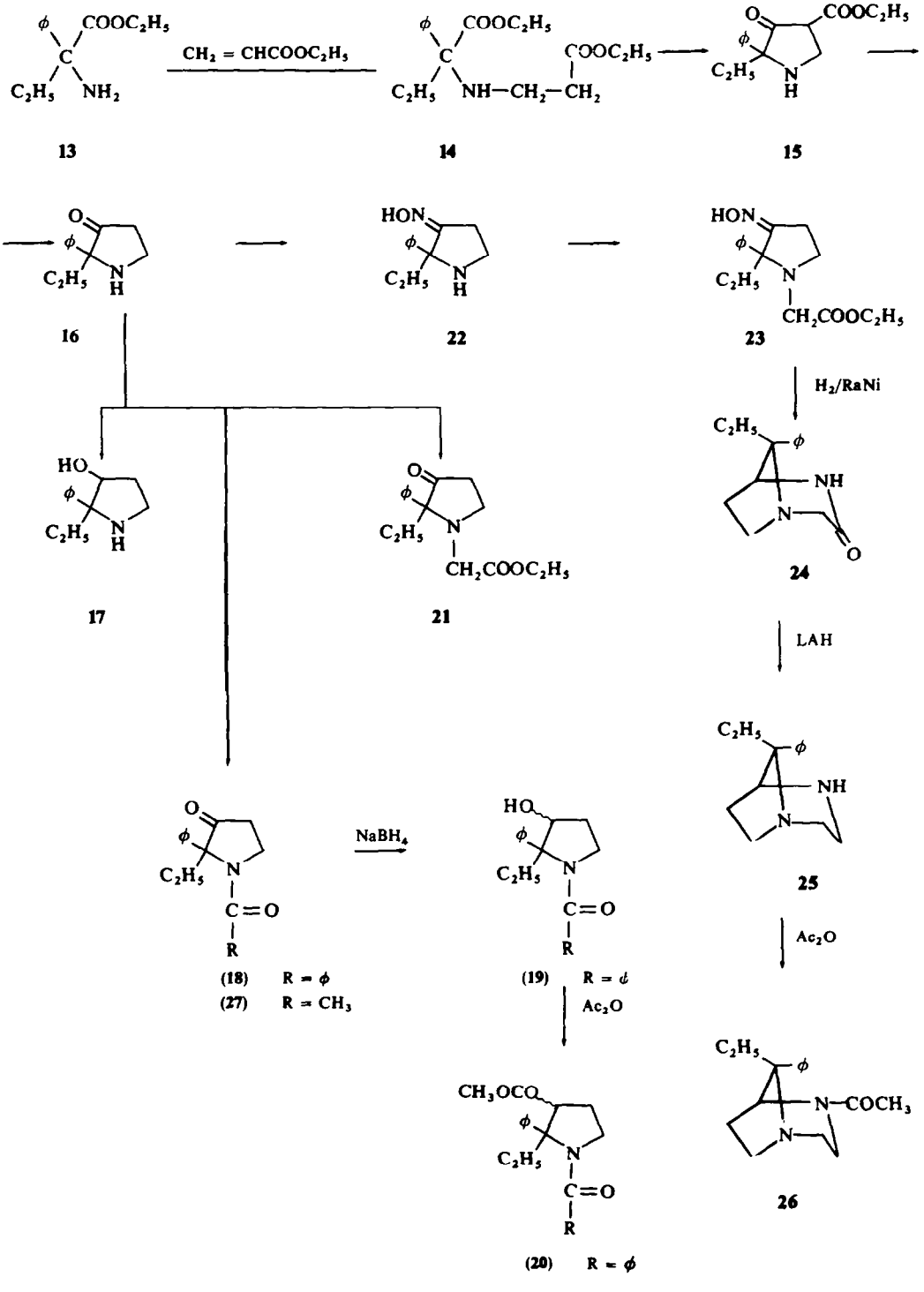
The last structural details of the bicyclic lactone **12** are the orientation of the Ph group and the conformation of the lactone ring. The formation of the *cis* 3-hydroxy-4-phenyl pyrrolidine derivative **9a** following the opening of the bicyclic system places [necessarily] the phenyl group in the *endo* configuration. As to the six-membered ring lactone, there are strong indications that it prefers the chair conformation, the carbonyl group pointing downwards (endo). In such a case, the carbonyl is far away from either one of the C-8 protons which do not differ therefore significantly in their chemical shifts.

Alkylation of α-phenyl-α-ethylglycine ethyl ester (**13**) with ethyl acrylate afforded the aminodiester **14** [N-(2-carbethoxyethyl)-α-phenyl-α-ethylglycine ethyl ester), yielding by Dieckmann condensation the unstable 2-phenyl-2-ethyl-4-carbethoxypyrrolidin-3-one, (**15**) which was immediately converted in presence of mineral acid into 2-phenyl-2-ethylpyrrolidin-3-one (**16**), ν_{max} 1745 cm^{-1}, in an overall yield of 86%. Upon reduction with $NaBH_4$ of the carbonyl group in the latter (**16**), the corresponding crystalline 2-phenyl-2-ethylpyrrolidin-3-ol **17**, m.p. 150–152° was obtained, displaying in its NMR spectrum a characteristic double doublet for the 3-H (δ 4·32, J = 5 and 2 Hz), suggestive of the preferential formation of only one of the two possible stereoisomeric alcohols. The relative configuration of this alcohol (**17**) has not been established.

The same reduction performed on the N-benzoyl derivative **18** afforded a mixture of the stereoisomeric alcohols (**19a** and **b**) in a ratio of 2:3, which were subsequently acetylated to the corresponding acetates (**20a** and **b**). Neither the alcohols nor their acetates could be separated; however the NMR of the latter displayed two OAc signals at δ 2·15 and 1·72 in the above ratio, and partly overlapped signals for the α to acetate proton (3-H) at δ 5·48 (double-doublet, J = 8 and 6 Hz) and δ 5·38 (double doublet, J = 5 and 3 Hz). According to the same criteria applied to the stereochemical assignments in the acetates **11a** and **b** the higher field signal (δ 1·72) has to be attributed to the *cis* stereoisomer (Ph and OAc). The aromatic solvent induced shifts ($\Delta^{CDCl_3}_{C_6H_6}$) measured for these signals (0·29 and 0·39 p.p.m. respectively) are in agreement with the corresponding solvent shifts measured for compounds **11a** and **b** (0·25 and 0·40 p.p.m. respectively).

The possibility that the hydride reduction had proceeded almost stereoselectively as in the case of **16** → **17** and that the observed NMR spectrum of the acetates **20a** and **b** is due actually to the conformational isomers arising through restricted rotation of the benzoyl group about the carbonyl carbon and the nitrogen was ruled out by a variable temperature analysis of this spectrum. The separation of the two acetate signals remained practically unchanged from 25° up to 120°.

SCHEME II. Synthesis of the bicyclic lactam **24**



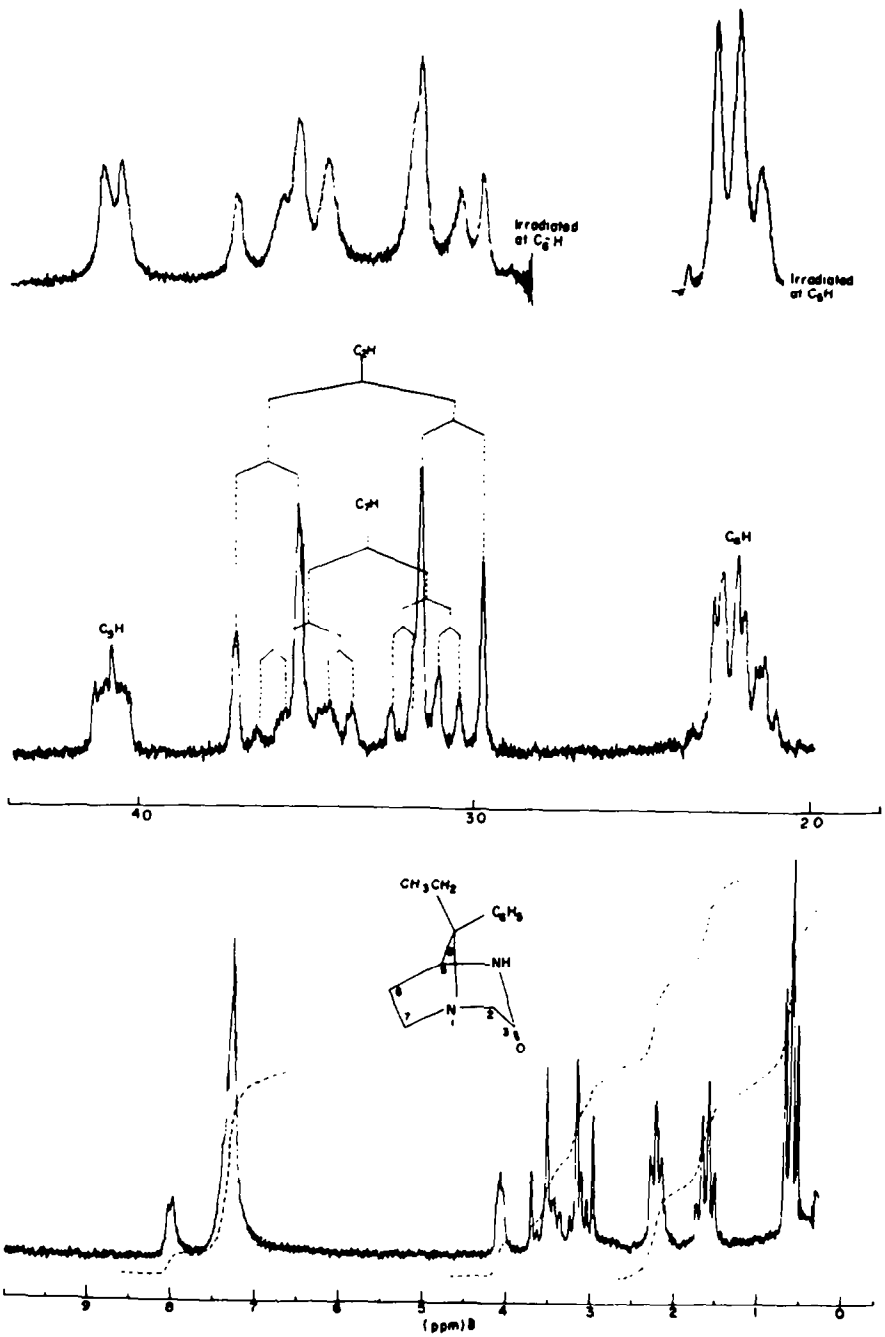


FIG 2. The NMR spectrum (100 MHz) of 8-phenyl-8-ethyl-1, 4-diazabicyclo[3.2.1]octan-3-one (**24**) in $CDCl_3$.

Treatment of **16** with ethyl bromoacetate in boiling xylene afforded the corresponding N-carbethoxymethyl derivative (**21**) which, according to the projected sequence should have led, following oximation (**23**) and reductive cyclisation, to the bicyclic lactam (**24**). This route was not however followed due to the low yield of the reaction (**16** → **21**; 28%) and the difficulties encountered in the separation by fractional distillation of **21** from unreacted **16**. The sequence was therefore reversed, i.e. the pyrrolidin-3-one (**16**) yielded with hydroxylamine the corresponding oxime (**22**) which was then N-alkylated to 2-phenyl-2-ethyl-(N-carbethoxymethyl) pyrrolidin-3-one oxime (**23**); catalytic reduction over Raney nickel at 80° and 15 atm. afforded directly, in 20% yield, the bicyclic lactam (**24**) (8-phenyl-8-ethyl-1,4-diazabicyclo [3. 2. 1] octan-3-one), m.p. 218°, characterised by the expected molecular weight (230, mass spectrometry), the IR absorption of the lactam carbonyl (1672 cm^{-1}), as well as by analysis of its NMR spectrum (Fig. 2).

The nonequivalent C-2 methylene protons adjacent to the C-3 carbonyl appear as an AB double doublet centered at δ 3·07 and 3·62 (J = 18 Hz). It is noteworthy that these protons possess the same splitting as in the bicyclic lactone **12**, but are significantly shifted upfield. The assignment is supported by the complete disappearance of their signals by exchange with deuterium, following treatment with C_2H_5OD/C_2H_5ONa.

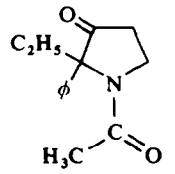
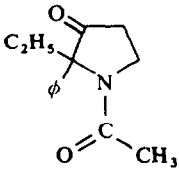
The two methylene groups at C-6 and C-7 give rise to complex patterns, narrow multiplet at δ 2·24 for the former and multiplet at δ 3·14 and 3·53 for the latter protons; the complexity of the signals is due to reciprocal splitting of these four protons as well as to coupling with the 5-H in the case of the C-6 methylene. Irradiation at the resonance position of the 5-H (δ 4·07) leads to a simplification of the narrow multiplet exhibited by the C-6 protons, being now split only by the neighbouring C-7 protons; conversely, irradiation at δ 2·24 (the C-6 multiplet) induces collapse of the δ 4·07 signal to a broadened doublet due to coupling with the amidic proton. Concomitantly, the signals of the C-7 protons are significantly simplified, appearing now as two AB doublets at δ 3·14 and 3·53 (J = 13 Hz), the former being most probably due to the *endo* 7-H and the latter to the *exo* 7-H. This assumption is based on the pattern of these signals before irradiation: the higher field doublet (J = 13 Hz) is additionally split by the *endo* 6-H to a double doublet (J = 6·5 Hz) slightly broadened by interaction with the *exo* 6-H (the dihedral angle between *endo* 7-H and *exo* 6-H is ~ 100°); the lower field doublet (δ 3·53) is additionally split by the *exo* 6-H (J = 7·7 Hz) and to a small extent by the *endo* 6-H.

The position of the C-8 Ph on the side of the lactam bridge as shown in **24** is supported by the upfield position of the C-2 protons as well as by the small difference between the chemical shifts of the C-6 protons, resulting in the δ 2·24 narrow multiplet.

LAH reduction[14] of the bicyclic lactam **24** afforded 8-phenyl-8-ethyl-1,4-diazabicyclo [3. 2. 1] octane (**25**), characterised as the corresponding dipicrate. Following acetylation, the N-acetate **26** was obtained as a viscous oil, characterised again as the crystalline picrate.

Acetylation of 2-phenyl-2-ethylpyrrolidin 3-one (**16**) afforded the corresponding crystalline amide (**27**) (N-acetyl-2-phenyl-2-ethylpyrrolidin-3-one) in 75% yield. The NMR spectrum at room temperature of this compound, in different solvents, pointed towards the presence of two conformational isomers, due to restricted rotation about the N—CO bond.

TABLE 2. NMR DATA FOR THE AMIDES **27a** AND **b** IN DIFFERENT SOLVENTS

		$CDCl_3$	C_6H_6	$CDBr_3$
 **27a**	CH_3CH_2- (tr)	0·88	0·55	0·90
	CH_3CO- (s)	1·77	1·55	1·82
	C_6H_5- (s)	7·34		7·33
 **27b**	CH_3CH_2- (tr)	0·81	0·69	0·80
	CH_3CO- (s)	2·27	1·74	2·40
	C_6H_5- (s)	7·30		7·27

It is noteworthy that the amidic Me group in **27a** is significantly upfield shifted (above or below the aromatic ring) as compared to the corresponding position of this signal in **27b**. By running the spectrum in the aromatic solvent, two contributing effects are disclosed: the shielding due to the intramolecular Ph group, working only on the amidic CH_3 in **27a** and the aromatic solvent induced shift, leading to the upfield shift of the amidic CH_3 in both conformational isomers.

The ratios of these isomers are solvent dependent: **27a**:**27b** ~ 4:3 in $CDCl_3$, ~ 3:4 in C_6D_6 and ~ 2:1 in $CDBr_3$.

The interpretation of the obtained NMR spectrum as being due to the presence of the conformational isomers **27a** and **27b** is based on the high temperature spectrum (140°, in $CDBr_3$) when all the above signals (Table 2) appeared as sharp patterns: triplet at δ 0·83 (CH_3CH_2–), singlet at δ 1·95 (CH_3CO) and singlet at δ 7·20 (C_6H_5). The coalescence temperature of the acetate signals is 95°. The original pattern of the conformational isomers was re-obtained by returning to room temperature.

EXPERIMENTAL

M.ps were taken on a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer infracord model 137 spectrophotometer equipped with a NaCl prism and refer to neat or to KBr pellets; NMR spectra were determined on Varian A-60 and HA-100 spectrometers for 5–10% solutions in $CDCl_3$ or other solvents, as specified, containing TMS as internal standard (we are grateful to Dr. Y. Kashman, the Tel-Aviv University, for the 100 MHz spectra and for the decoupling experiments). Mass spectra were taken with an Atlas CH4 instrument.

Microanalyses were carried out in the microanalytical laboratory of the Weizmann Institute under the direction of Mr. R. Heller.

(N-Carbethoxymethyl)-α-phenyl-α-ethyl-β-alanine ethyl ester (**2**). A chlf solution (100 ml) of α-phenyl-α-ethyl-β-alanine ethyl ester[15] (44·2 g, 0·2 moles) and ethyl chloroacetate (28·5 g, 0·23 moles) was heated to reflux for 24 hr with stirring, in the presence of K_2CO_3 (27 g) using a Stark-Dean trap. Following filtration, the solvent was removed and the residue distilled at 140–148°/0·15 mm to give **2** (52·5 g, 85% yield); ν_{max} 1750 cm^{-1}; NMR: δ 7·19 (s), C_6H_5; 4·09 (q) CH_3CH_2O-; 3·21 (s) $-HN-CH_2CO-$; 3·08 (s) $-HNCH_2-C-$; 2·11 (m), CH_3CH_2C; 1·60 (m) $-NH-$; 1·23 (tr) CH_3CH_2O-; 1·15 (tr) CH_3CH_2O; 0·78 (tr) CH_3CH_2C; (Found: C, 66·73; H, 8·42; N, 4·43. $C_{17}H_{25}NO_4$ requires: C, 66·42; H, 8·20; N, 4·56%).

4-Phenyl-4-ethylpyrrolidine-3-one (**4**). A solution of **2** (30·8 g, 0·1 moles) in dry toluene (150 ml) was

added dropwise at 70°, to a stirred suspension of NaH (0·22 moles, 50% mineral oil suspension) in dry toluene (50 ml). The stirring was continued for 90 min at reflux. After cooling (salt ice bath), the calculated amount of aq. AcOH (1:3) was slowly added, the precipitate filtered and the solvent removed *in vacuo*. The residue, which gave a positive test with $FeCl_3$, was immediately submitted, without any purification, to acid catalysed hydrolysis and ensuing decarboxylation by refluxing it during 90 min with 6N HCl (150 ml). After cooling and filtration the solution was extracted with C_6H_6 to remove paraffin oil and non-aminic byproducts; the acidic aq. solution was then treated with aq. NaOH to pH 12, the product extracted with $CHCl_3$, washed with water, dried ($MgSO_4$), and the solvent removed; the residue distilled at 108°/0·1 mm (10·5 g, 57%), as a colourless liquid which had to be preserved at low temp; ν_{max} 1695 cm^{-1} (Found: C, 76·17; H, 7·78; N, 7·63. $C_{12}H_{15}NO$ requires: C, 76·15; H, 7·99; N, 7·40%).

The oxime (**5**) m.p. 137–138° (from methylcyclohexane) was prepared with H_2NOH. HCl neutralised with ethanolic NaOEt. (Found: C, 70·64; H, 7·97; N, 13·89. $C_{12}H_{16}N_2O$ requires: C, 70·56; H, 7·90; N, 13·72%).

(N-Carbethoxymethyl)-4-phenyl-4-ethylpyrrolidin-3-one (**6**). To a solution of **4** (11·65 g, 0·06 moles) in toluene (50 ml), ethyl bromoacetate (0·08 moles) and K_2CO_3 (0·09 moles) were added, the mixture heated under reflux for 15 hr with stirring and azeotropic removal of water, then filtered, the solvent removed and the residue distilled at 145–148°/0·2 mm to give **6** (8·8 g, 53%); ν_{max} 1730 and 1750 cm^{-1}. (Found: C, 70·51; H, 7·82; N, 5·57. $C_{16}H_{21}NO_3$ requires: C, 69·79; H, 7·69; N, 5·09%).

(N-Carbethoxymethyl)-4-phenyl-4-ethylpyrrolidin-3-ol (**7**). $NaBH_4$ (1 g) was added portionwise at r.t. to an ethanolic solution (50 ml) of **6** (2·7 g). After stirring for 2 hr, the solution was cooled and AcOH (2 ml) added dropwise; after removing the solvent in vacuo, the residue was dissolved in dilute HCl and byproducts extracted with C_6H_6; the aq. solution was then made alkaline and reextracted with $CHCl_3$. After washing and drying ($MgSO_4$) the solvent was removed and the residue distilled at 130°/0·1 mm (1·9 g, 70%). The product showed two distinct spots on a TLC plate (EtOAC), corresponding to the stereoisomeric alcohols **7**. Separation was achieved by column chromatography on silicagel (0·05–0·2 mm) and elution with hexane–ether (6:4); the *trans* compound **7b** emerged first. The analysis was performed on the mixture. (Found: C, 69·08; H, 8·28; N, 4·99. $C_{16}H_{23}NO_3$ requires: C, 69·28; H, 8·36; N, 5·03%).

4-Phenyl-4-ethylpyrrolidin-3-ol (**8**). The reduction of **4** (3.76 g) was performed with $NaBH_4$ (1·5 g) as described above (**6** → **7**). The crude product was separated by crystallization from petroleum ether, yielding the crystalline **8a** (0·8 g), m.p. 122° (pet. ether). (Found: C, 75·29; H, 8·80; N, 7·39. $C_{12}H_{17}NO$ requires: C, 75·35; H, 8·96; N, 7·32%). The mother liquors from the crystallization yielded upon evaporation of the solvent and distillation *in vacuo* the second isomer **8b**, b.p. 127°/0·2 mm (2 g). (Found: C, 75·24; H, 9·13; N, 7·37%).

Alkylation of the stereoisomeric mixture **8** *to* **7** *and* **9**. To a $CHCl_3$ solution (30 ml) of **8** (2 g), ethyl chloroacetate (2 g) and K_2CO_3 (2 g) was added and the mixture submitted to the same treatment as described above (**4** → **6**), to yield a mixture of **7a** and **7b** (total yield 71%).

Similarly, by use of methyl chloroacetate, a mixture of the methyl esters **9a** + **9b** was obtained (74%) distilling at 145°/0·15 mm. Separation was achieved by chromatography on silicagel and elution with hexane–ether 6:4. The analysis was performed on the mixture (Found: C, 68·04; H, 8·02; N, 5·16. $C_{15}H_{21}NO_3$ requires: C, 68·41; H, 8·04; N, 5·32%).

Acetylation of the hydroxyester **9a** *to (N-carbethoxymethyl)-3-acetoxy-4-phenyl-4-ethylpyrrolidine* (**11a**) *and of* **9b** *to* **11b**. The hydroxyester **9a** (1·6 g) was kept overnight in a mixture of Ac_2O (2·5 g) and dry pyridine (5 ml), the excess reagents were removed *in vacuo*, the residue dissolved in dilute HCl, impurities extracted with C_6H_6 the aq. solution decolorized by means of charcoal, filtered, added an excess of cold aq. Na_2CO_3 and extracted with $CHCl_3$. After drying over $MgSO_4$, the solvent was removed and the residue distilled *in vacuo* to give **11b** (1·4 g), b.p. 145°/0·2 mm. ν_{max} 1730 cm^{-1}. (Found: C, 66·73; H, 7·89; N, 4·71. $C_{17}H_{25}NO_3$ requires: C, 66·42; H, 8·20; N, 4·56%).

Similarly acetylation of **9b** afforded **11b**, b.p. 140°/0·15 mm. (Found: C, 66·53; H, 8·35; N, 4·62).

6-Phenyl-6-ethyl-1-aza-4-oxabicyclo[3.2.1]*octan-3-one* (**12**). a. *By cyclization of the mixture of hydroxy acids* **10** (**a** + **b**). A mixture of the ethyl esters **7** (**a** + **b**) in 2N aq. HCl was refluxed during 4 hr. After evaporation to dryness, the residue (3.2 g) was dissolved in conc. H_2SO_4 (10 ml), left at r.t. for 48 hr, poured onto ice (70 g), treated with active charcoal and filtered. After neutralizing the solution by means of $NaHCO_3$, the oily layer was extracted with $CHCl_3$, the solution washed with water, dried and evaporated to dryness. The bicyclic lactone **12** crystallized upon adding petroleum ether. Recrystallization from this solvent afforded pure **12** (0·02 g), m.p. 123°, ν_{max} 1730 cm^{-1}. (Found: C, 72·61; H, 7·13; N, 5·95; M, 231. $C_{14}H_{17}NO_2$ requires: C, 72·70; H, 7·41; N, 6·06; MW, 231).

b. *By cyclization of the hydroxyester* **9a**. A solution of **9a** (0·41 g) in dry toluene (50 ml) to which conc H_2SO_4 (1 g) was added, was heated to reflux for 12 hr with stirring and azeotropic removal of water. The mixture was poured onto ice, the aqueous layer separated, washed with toluene, decolorised (charcoal), filtered, and made alkaline with aq. $NaHCO_3$. The reaction product was extracted with $CHCl_3$. After removing the solvent the residue was recrystallized from petroleum ether to yield **12** (0·4 g, 12%) m.p. 123°, showing no depression when mixed with the product obtained by the alternative method given above. **12** was equally obtained from the hydroxyester **9b**, (10% yield), from each of the acetoxyesters **11a** and **11b** (12%) and from the mixture of hydroxyesters **7a** + **b** (11%).

Methanolysis of **12** *to the hydroxyester* **9a**. The bicyclic lactone **12** (0·075 g) was dissolved in MeOH containing a catalytic amount of MeONa (10 ml MeOH and *ca.* 5 mg of Na). The progress of the reaction was followed by TLC (gradual disappearance of the spot of **12** and appearance of a higher spot showing the same R_f as the hydroxyester **9a**. Methanolysis was complete after 6 hr. The solvent was removed and the crude residue identified by direct comparison with **9a**. Acetylation of the product afforded the acetate **11a**, again identified by direct comparison. The reaction proceeded quantitatively.

2-Phenyl-2-ethyl-4-carbethoxypyrrolidine-3-one (**15**). This compound was prepared from α-phenyl-α-ethyl glycine ethyl ester[16] (**13**), following the scheme developed by Dr. Uri Golik of this laboratory.[8]

a. *Alkylation of* **13** *with ethyl acrylate*. A solution of **13** (54 g, 0·2 moles) and ethyl acrylate (70 g) in EtOH (250 ml) containing Triton B (1 ml) was kept in an autoclave at 70° during 160 hours. Distillation of the reaction product afforded N(2-carbethoxyethyl)-α-phenyl-α-ethylglycine ethyl ester (**14**) in 61% yield $b.p._{0·1}$ 144–150°; ν_{max} 1738 cm^{-1}. (Found: C, 66·50; H, 8·15; N, 4·77. $C_{17}H_{25}NO_4$ requires: C, 66·42; H, 8·20; N, 4·56%.

b. *Dieckmann condensation of* **14** *to* **15**. A suspension of C_2H_5ONa in dry toluene (200 ml) was prepared from Na (2·5 g) in abs EtOH (50 ml), the EtOH removed by distillation and then gradually replaced by toluene; the distillation was continued under stirring until the last traces of EtOH were removed. To this stirred suspension a solution of **14** (32·5 g) in toluene (50 ml) was added dropwise at 70°. Heating was continued while distilling off the EtOH formed during the cyclisation using a special column head. The heating was discontinued when the temperature at the column head reached 110°. After cooling (ice salt bath) ice water (300 ml) was dropwise added keeping the temperature below 5°. The aq. layer was acidified with AcOH, the reaction product extracted with $CHCl_3$, washed with $NaHCO_3$ solution and water. After drying over $MgSO_4$ the solvent was removed *in vacuo*. The residue (22 g) was not further purified; positive $FeCl_3$ test, one spot on a TLC plate.

2-Phenyl-2-ethylpyrrolidin-3-one (**16**). A solution of **15** (20 g) in 6N HCl (150 ml) was heated to reflux during 2 hr, cooled and made alkaline with conc. aq. NaOH. The reaction product was extracted with $CHCl_3$, washed and dried. The solvent was removed and the residue distilled *in vacuo*, collecting the fraction passing at 88–92°/0·1 mm (12·5 g); ν_{max} 1745 cm^{-1}. (Found: C, 75·84; H, 8·05; N, 7·30. $C_{12}H_{15}NO$ requires: C, 76·15; H, 7·99; N, 7·40%).

2-Phenyl-2-ethylpyrrolidin-3-ol (**17**). To a solution of **16** (5 g) in EtOH (50 ml), $NaBH_4$ (1·3 g) was added in small portions. After 2 hr at r.t. the solution was acidified with AcOH, the solvent removed, the residue dissolved in dilute HCl, treated with charcoal and filtered. Then, solution was neutralized with aq. $NaHCO_3$ setting free the amine **17** which crystallized immediately. Recrystallization from benzene afforded pure **17** (4·5 g), m.p. 150–152°. (Found: C, 75·22; H, 8·98; N, 7·17. $C_{12}H_{17}NO$ requires: C, 75·35; H, 8·96; N, 7·32%).

N-Benzoyl-2-phenyl-2-ethylpyrrolidin-3-one (**18**). A mixture of **16** (0·9 g), benzoyl chloride (2 ml) and 2N aq. NaOH (25 ml) was shaken during 1½ hr at r.t. The crystalline precipitate was filtered, washed with water and recrystallized from EtOH, m.p. 142–145° (1·3 g); ν_{max} 1748 and 1634 cm^{-1}. (Found: C, 77·82; H, 6·59; N, 4·82. $C_{19}H_{19}NO_2$ requires: C, 77·79; H, 6·53; N, 4·77%).

N-Benzoyl-2-phenyl-2-ethylpyrrolidin-3-ol (**19a** + **b**). To a solution of **18** (1·1 g) in EtOH (25 ml), $NaBH_4$ (0·15 g) was added; after 4 hr the mixture was worked up as above (**16** → **17**) and the product distilled at 190–210°/0·3 mm to give a mixture of the stereoisomeric 3-ols.

Acetylation of the mixture afforded the corresponding acetates (**20a** + **b**) which could not be separated. Their characterization is based upon the analysis of the NMR spectrum.

N-(Carbethoxymethyl)-2-phenyl-2-ethylpyrrolidin-3-one (**21**). A mixture of **16** (1 g), ethyl bromoacetate (2 ml) and K_2CO_3 (2 g) in xylene (70 ml) was heated for 24 hr under reflux using a Stark-Dean trap to remove the water formed in the reaction. After cooling and filtration the solution was treated with dilute HCl, the aq. solution made alkaline with $NaHCO_3$, extracted with C_6H_6, washed and dried. The solvent was removed and the residue was distilled *in vacuo* yielding first unreacted **16** (0·4 g), followed by **21** which

distilled at 132°/0·2 mm (0·2 g); ν_{max} 1745, 1751 cm^{-1}; NMR characteristic for the $-CH_2COOCH_2CH_3$ moiety. (Found: C, 69·51; H, 7·53; N, 4·87. $C_{16}H_{21}NO_3$ requires: C, 69·79; H, 7·69; N, 5·09%).

2-Phenyl-2-ethylpyrrolidin-3-one oxime (**22**). To a solution of $NH_2OH.HCl$ (4·1 g) in EtOH (100 ml) an ethanolic C_2H_5ONa solution (5% excess) was added, followed by a solution of **16** (8·3 g) in EtOH (20 ml). After refluxing during 2 hr, the solvent was removed, the residue dissolved in $CHCl_3$, washed, dried, the solvent removed and the residue recrystallized from hexane, m.p. 95–96° (7·9 g). (Found: C, 70·81; H, 8·04; N, 13·50. $C_{12}H_{16}N_2O$ requires: C, 70·65; H, 7·90; N, 13·72%).

N-(Carbethoxymethyl)-2-phenyl-2-ethylpyrrolidin-3-one oxime (**23**). The reaction was performed with **22** (8·5 g) and ethyl bromoacetate in xylene as described above (**16** → **21**). The obtained product (**23**) distilled at 170–180°/0·35 mm (6·9 g). (Found: C, 65·38; H, 7·18; N, 9·63. $C_{15}H_{20}N_2O_3$ requires: C, 65·19; H, 7·30; N, 10·14%).

8-Phenyl-8-ethyl-1,4-diazabicyclo[3.2.1]*octan-3-one* (**24**). The oxime **23** (2·3 g) in EtOH (20 ml) was reduced by means of H_2 at 16 atm and 80° in the presence of Raney (Ni (~1 g), during 24 hr. The solution was filtered, the solvent removed and the residue recrystallized several times from C_6H_6 to give **24** (0·37 g), m.p. 218°; ν_{max} 1672 cm^{-1}. (Found: C, 73·32; H, 8·03; N, 11·96; M^+ 230. $C_{14}H_{18}N_2O$ requires: C, 73·01; H, 7·88; N, 12·17%, M. W. 230).

8-Phenyl-8-ethyl-1,4-diazabicyclo[3.2.1]*octane* (**25**). To a suspension of LAH (0·1 g) in dry THF (20 ml) a solution of **25** (0·2 g) in the same solvent (2 ml) was added, the mixture stirred for 1 hr at r.t. and 8 hr at reflux, then colled and the excess reagent decomposed with EtOAc and Na_2SO_4. The reaction product was isolated by extraction with $CHCl_3$, washed, the solvent removed and the residue identified by formation of the crystalline dipicrate, m.p. 245° (EtOH). The IR spectrum of crude **25** did not show any carbonyl absorption. (Found for the dipicrate: C, 46·08; H, 4·18; N, 16·45. $C_{26}H_{26}N_8O_{14}$ requires: C, 46·29; H, 3·88; N, 16·66%).

Acetylation of **25** with Ac_2O/pyridine afforded the oily monoacetate **26** [4-acetyl-8-phenyl-8-ethyl-1, 4-diazabicyclo[3. 2. 1]octane, ν_{max} 1640 cm^{-1}; picrate, m.p. 176–179° (EtOH). (Found for the picrate: C, 54·00; H, 5·07; N, 14·20. $C_{22}H_{25}N_5O_8$ requires: C, 54·20; H, 5·17; N, 14·37%).

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